Transplant Therapy for Type 1 Diabetes Mellitus

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Insulin-dependent diabetes mellitus is a devastating disease affecting more than one million patients in the United States alone. While advances have been made in exogenous insulin therapy, pancreas transplantation remains the only available treatment that restores a euglycemic state, a consistently normal glycosylated hemoglobin level, and functioning biofeedback regulatory control. New immunosuppressive regimens and improvements in surgical technique have resulted in improved patient and pancreas graft survival rates. Recent advances in islet cell purification and immunosuppressive therapies aimed at reducing rejection have renewed interest in islet cell transplantation.

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Type 1 diabetes mellitus results in insulin deficiency, hyperglycemia, and death unless exogenous insulin is provided. Currently, more than one million individuals in the United States have been diagnosed with insulin-dependent or type 1 diabetes mellitus, and approximately 30,000 new cases are identified each year (1). Despite therapy with exogenous insulin, over 50% of patients with type 1 diabetes will develop serious end-organ complications such as nephropathy, retinopathy, neuropathy, or atherosclerosis, which in turn result in significant morbidity and premature death and impart a huge financial cost to society. With long-term disease progression, at least 30% of diabetics will develop blindness, more than 60% will suffer from clinically significant neuropathy, and 40% will develop renal failure (1-4). Type 1 diabetes is now the leading cause of end-stage renal disease in the United States, accounting for nearly 30% of cases. Approximately 80% of type 1 patients will eventually die of cardiovascular complications of their disease, resulting in a life expectancy approximately one-third less than that of the general population (1-4).

Rationale for Pancreas Transplantation

The goals of therapy for patients with type 1 diabetes are to establish euglycemia, reduce the incidence and severity of secondary complications, improve the patient's quality of life, and reduce premature death. Frequent glucose monitoring with multiple insulin injections and continuous insulin infusion pump systems result in near physiologic glucose metabolism in many patients. Benefits of tight control of glucose metabolism include reducing secondary complications. The Diabetes Complication and Control Trial (DCCT) definitively demonstrated that the maintenance of near normal glycemia reduces the prevalence of nephropathy, neuropathy, and retinopathy by as much as 50% (2). If a euglycemic state can be achieved early in the course of diabetes, secondary complications may not occur. While the benefits of tight glucose control are clear, the necessary regimens are associated with an increased risk of insulin overdose with resulting hypoglycemic coma, as well as patient noncompliance due to the rigorous demands of frequent glucose monitoring over time.

The difficulty in achieving consistently tight glucose control using exogenous insulin has led to an increased focus on pancreas transplantation as the principal therapy for patients with type 1 diabetes. Since pancreas transplantation normalizes glucose metabolism to a far greater extent than even the most rigorous of exogenous insulin regimens, it is hypothesized that pancreas transplantation slows the progression of diabetic complications even more effectively than results achieved in the DCCT.

Pancreas Transplantation Decreases Diabetic Complications

While large-scale randomized trials are lacking, there is mounting evidence that pancreas transplantation does in fact limit the progression of the secondary complications of type 1 diabetes.

Recent data suggest that pancreas transplantation alone can halt and even reverse lesions of diabetic nephropathy (5), and a pancreas transplanted synchronously with a kidney protects the new renal allograft from the deleterious effects of type 1 diabetes (6). While improvements in diabetic retinopathy have been difficult to demonstrate (7), stabilization of retinopathy has been reported (8,9). Improvements in nerve conduction and autonomic function have been unequivocally observed (3,10). Indeed, 10-year patient survival rates are significantly higher for those patients with end-stage diabetic nephropathy who receive synchronous pancreas-kidney transplants versus those who receive a kidney transplant alone (11).

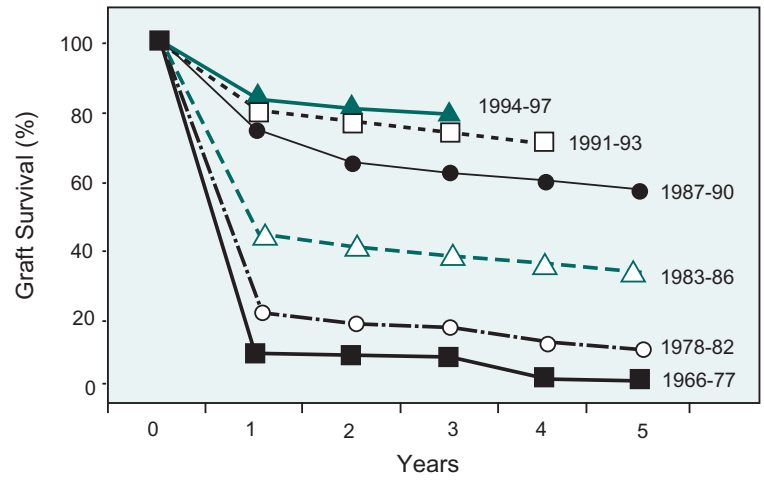


Figure 1. Pancreas allograft graft survival by era.

The Quality of Life Issues in Pancreas Transplantation

While a reduction in the prevalence of secondary diabetic complications and the potential increase in long-term patient survival are valid reasons for pursuing pancreas transplantation, quality of life issues are often dominant in the minds of potential recipients (12). Intense insulin therapy in concert with strict dietary restrictions is a cumbersome and time-consuming process requiring multiple finger sticks and insulin injections each day. Despite diligent monitoring of dietary intake, physical activity, and blood glucose levels, a euglycemic state is never achieved. Moreover, the patient still faces the potential life-threatening complications of insulin deficiency and excess, which include diabetic ketoacidosis and hypoglycemic unawareness. With improved immunosuppression regimens and advances in surgical techniques resulting in higher patient and graft survival rates, pancreas transplantation is now performed by some centers with the primary purpose of achieving independence from exogenous insulin. In other words, the risks of exogenous insulin therapy and the associated restrictions of life-style are traded for the risks of surgery and life-long immunosuppression and an improved quality of life.

Current Practices and Results

According to the International Pancreas Transplant Registry (13,14), over 9000 pancreas transplants have been performed in the United States, with current annual totals of more than 1000 cases. The vast majority of these were performed as synchronous pancreas-kidney transplants (SPK) with a trend toward an increased number of pancreas after kidney transplants (PAK). In 1998-1999, the proportion of pancreas transplants performed as PAK transplants exceeded the 10% mark for the first time. Pancreas transplants alone (PTA) continue to account for than less than 5% of transplants performed per year, and living-donor partial pancreas transplants, a technique pioneered at the University of Minnesota, account for less than 1% (13-15).

Over the past 15 years, patient and graft survival rates have improved dramatically (Figure 1). One-year patient and pancreas graft survival rates for SPK cases performed in 1996-1997 were 95% and 85%, respectively. For PAK transplants performed in the same period, 1-year patient survival was 90% while pancreas graft survival was 74%. One-year patient survival for PTA performed in 1996-1997 was 96% with a 1-year pancreas graft survival rate of 69% (13,14). These results have spurred enthusiasm for pancreas transplant therapy in carefully selected patients.

Patient Selection

While in the future pancreas transplantation may be geared more toward diabetic patients without established end-organ disease, currently, most pancreas transplant recipients are long-term diabetics with end-stage renal disease who receive an accompanying kidney transplant. These dialysis-dependent patients have already accepted the risks of long-term immunosuppressive therapy as a component of their kidney transplant. The addition of a pancreas transplant, while adding somewhat to the magnitude of the surgical procedure, requires no additional immunosuppression.

The majority of transplant centers restrict pancreas transplantation to type 1 diabetes patients, who are C-peptide negative. Recently, however, selected type 2 diabetes patients have received pancreas transplants. Between 1994 and 1999, 4% of the pancreas transplants performed in the US were for patients described as having type 2 diabetes. Patient, graft, and insulin-independence rates were not significantly different for type 2 versus type 1 pancreas allograft recipients (14).

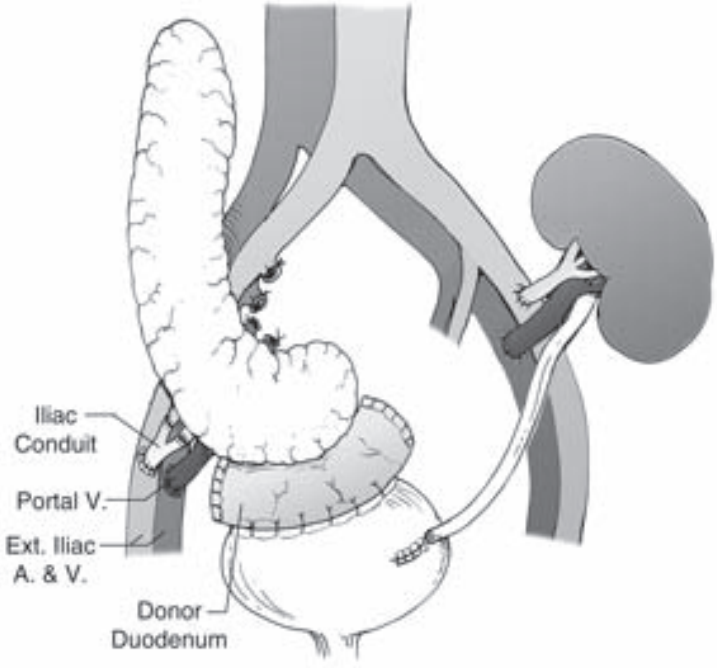


Figure 2. Combined pancreas/kidney transplant using standard bladder/systemic technique.

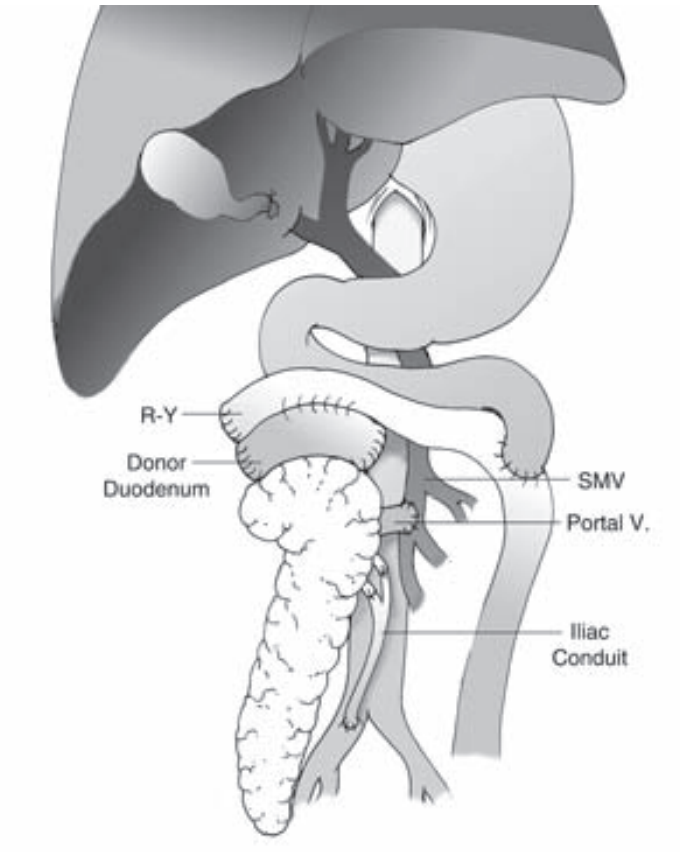


Figure 3. Pancreas transplant using enteric/portal technique. R-Y = Roux-en-Y, SMV = superior mesenteric vein.

Absolute contraindications to pancreas transplantation include malignancy, active infection, or a history of noncompliance. Relative contraindications include severe cardiopulmonary disease that would interfere with the patient's ability to safely undergo transplant surgery. While blindness and amputation are not absolute contraindications, the patient must have adequate functional status with potential to benefit substantially from the transplant. There are no absolute age restrictions, but recipients are generally under 55 years of age.

Bladder vs. Enteric Exocrine Drainage

Though the pancreas is transplanted for its endocrine function, management of its exocrine drainage remains a significant problem and accounts for a large percentage of complications seen with pancreas transplantation. Historically, the most commonly used technique for managing exocrine pancreatic secretions has been bladder drainage (Figure 2), but, over the past few years, a renewed interest in enteric drainage has occurred (Figure 3). In 1996, 31% of all pancreas transplants performed used enteric drainage, more than 10 times the frequency used in 1990 (13). In 1998, the proportion increased to 60% (14). While pancreas allograft and patient survival are similar for the two techniques, enteric drainage avoids the frequently encountered problems of cystitis, urinary tract infection, reflux pancreatitis, metabolic acidosis, hematuria, and dehydration associated with bladder drainage. Fewer complications translate into fewer patient hospital days and increased patient satisfaction (13,14).

Portal vs. Systemic Endocrine Drainage

The classic technique used for pancreatic endocrine drainage directs venous outflow from the pancreas allograft to the recipient iliac vein (Figure 2). This endocrine drainage into the systemic circulation results in hyperinsulinemia, which may be associated with accelerated atherosclerosis. While the clinical significance of hyperinsulinemia is uncertain, this concern has led to a technique using portal venous drainage via the superior mesenteric vein (Figure 3) (16). More than 20% of pancreas transplants performed in 1999 used the portal venous drainage technique (14). Besides providing venous outflow similar to that of a native pancreas, portal venous drainage has the theoretical advantage of delivering allograft antigens to the liver. Delivery of antigens to the liver by the portal vein has been associated with the induction of immunotolerance. Indeed, initial reports suggest that rejection rates are less in pancreases drained using the portal technique versus those using the usual systemic technique (3,17).

Immunosuppression

Whole pancreas transplantation requires life-long immunosuppression. The majority of transplant centers use a multidrug regimen anchored by either cyclosporine or tacrolimus in combination with mycophenolic acid and corticosteroids (4,14). Between 1996 and 1999, nearly two-thirds of pancreas recipients received induction anti-T cell therapy (14). The introduction of newer agents, such as sirolimus and anti-interleukin-2 receptor antibodies, promises to change established immunosuppression practices with the goal of lessening immunologic graft failure as well as reducing the rate of infectious complications.

Islet Cell Transplantation

While pancreas transplantation has proven to be a successful procedure, its widespread application has been hampered by the complications associated with major abdominal surgery, particularly those related to the handling of the exocrine component of the gland. For these reasons, islet cell transplantation has been proposed as a more favorable way to cure diabetes. Though islet cell transplantation would have many advantages over whole organ pancreas transplantation, more than 2 decades of clinical experience with islet cell transplants have yielded disappointing results. According to the International Islet Transplant Registry, only 8.2% of patients who received an islet cell transplant between 1990 and 1998 remained insulin independent for more than 1 year (18). Factors limiting success likely included insufficient islet cell number and purity as well as dependence on immunosuppression drugs which themselves are diabetogenic (19).

Improved islet isolation techniques (20) and the introduction of new immunosuppression agents have sparked a renewed interest in islet cell transplantation. Researchers in Edmonton, Canada have recently reported clinical success (21). The Edmonton group used a corticosteroid-free immunosuppression regimen of sirolimus, low-dose tacrolimus, and anti-interleukin-2 receptor antibody. This regimen was not diabetogenic and provided enough immunosuppression to both prevent rejection and avoid autoimmune destruction of transplanted islets. All seven patients studied achieved insulin independence with a mean follow-up of nearly 1 year. However, the number of islets needed to achieve this success was nearly double that previously reported, requiring more than one donor pancreas in each recipient. Nevertheless, after years of dismal results, this success is remarkable.

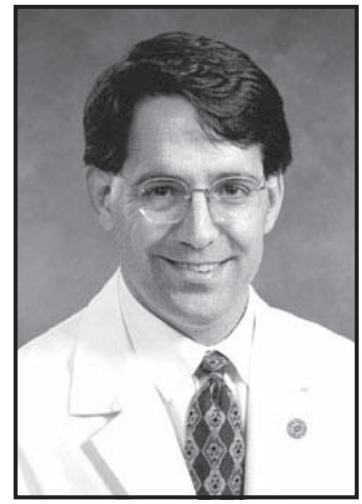
Summary

Clearly, with only 6000 suitable cadaveric pancreas allografts available in the United States each year, for the foreseeable future, transplant therapy for type 1 diabetes will remain an option for only a small number of patients. But significant progress has been made in the last decade, and a solid foundation for the future is in place. Cultured islets or beta cells, embryonic beta stem cells, and xenogeneic islet cells or whole organs each could circumvent the problem of a cadaveric organ shortage. Research continues on these and a wide variety of projects, making the future of transplant therapy for type 1 diabetes very interesting, indeed.

References

1. Stratta RJ. Mortality after vascularized pancreas transplantation. Surgery 1998;124:823-830.
2. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. N Engl J Med 1993; 329:977-986.
3. Hricik DE. Combined kidney-pancreas transplantation. Kidney Int 1998; 53:1091-1102.
4. Bruce DS, Woodle ES, Newell KA, et al. Tacrolimus/mycophenolate provides superior immunosuppression relative to neoral/mycophenolate in synchronous pancreas-kidney transplantation. Transplant Proc 1998; 30:1538-1540.
5. Fioretto P, Steffes MW, Sutherland DE, et al. Reversal of lesions of diabetic nephropathy after pancreas transplantation. N Engl J Med 1998; 339:69-75.
6. Wilczek HE, Jaremko G, Tyden G, et al. Evolution of diabetic nephropathy in kidney grafts. Evidence that a simultaneously transplanted pancreas exerts a protective effect. Transplantation 1995; 59:51-57.
7. Ramsay RC, Goetz FC, Sutherland DE, et al. Progression of diabetic retinopathy after pancreas transplantation for insulin-dependent diabetes mellitus. N Engl J Med 1988; 318:208-214.
8. Chow VC, Pai RP, Chapman JR, et al. Diabetic retinopathy after combined kidney-pancreas transplantation. Clin Transplant 1999; 13:356-362.
9. Kennedy WR, Navarro X, Goetz FC, et al. Effects of pancreatic transplantation on diabetic neuropathy. N Engl J Med 1990; 322:1031-1037.
10. Koznarova R, Saudek F, Sosna T, et al. Beneficial effect of pancreas and kidney transplantation on advanced diabetic retinopathy. Cell Transplant 2000; 9:903-908.
11. Tyden G, Bolinder J, Solders G, et al. Improved survival in patients with insulin-dependent diabetes mellitus and end-stage diabetic nephropathy 10 years after combined pancreas and kidney transplantation. Transplantation 1999; 67:645-648.
12. Gross CR, Limwattananon C, Matthees BJ. Quality of life after pancreas transplantation: a review. Clin Transplant 1998; 12:351-361.

13. Gruessner AC, Sutherland DE, Gruessner RW. Report of the International Transplant Registry. Transplant Proc 1998; 30:242-243.
14. Gruessner AC, Sutherland DE. Analyses of pancreas transplant outcomes for United States reported to the United Network for Organ Sharing (UNOS) and non-US cases reported to The International Pancreas Transplant Registry (IPTR). Clin Transpl 1999; 51-69.
15. Sutherland DER, Najarian JS, Gruessner RG. Living versus cadaver donor pancreas transplants. Trans Proceedings 1998; 30:2264-2266.
16. Gaber AO, Shokouh-Amiri H, Grewal HP, et al. A technique for portal pancreatic transplantation with enteric drainage. Surg Gynecol Obstet 1993; 177:417-419.
17. Nymann T, Hathaway DK, Shokouh-Amiri MH. Patterns of acute rejection in portal-enteric versus systemic-bladder pancreas-kidney transplantation. Clin Transplant 1998; 12:175-183.
18. Berney T, Ricordi C. Islet cell transplantation: the future? Langenbech Arch Surg 2000;385:373-378.
19. Hering BJ, Ricordi C. Islet transplantation for patients with type 1 diabetes. Graft 1999; 2: 12-27.
20. Linetsky E, Bottino R, Lehmann R, et al. Improved human islet isolation using a new enzyme blend, liberase. Diabetes 1997; 46:1120-1123.
21. Shapiro AM, Lakey JR, Ryan EA, et al. Islet transplantation in seven patients with type 1 diabetes mellitus using a glucocorticoid-free immunosuppressive regimen. N Engl J Med 2000; 343:230-238.



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